IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Division Under 37 C.F.R. 1.53(b)
Application of: Maruani et al.

Prior Application Serial No.: 09/341,764

Prior Filing Date: August 19, 1999

Prior Group Art Unit: 1617

Anticipated Classification of this Application:
Class 514 Subclass 406.000

Examiner: J. Kim

For: USE OF CANNABINOID RECEPTOR ANTAGONISTS FOR THE PREPARATION OF DRUGS

CERTIFICATE UNDER 37 C.F.R. 1.10

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Commissioner for Patents
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Dear Sir:

PRELIMINARY AMENDMENT

Please amend the above-identified application as follows:

In the specification:

On page 1, after the title of the invention and before line 2, insert the following cross reference to related application information:

--Cross Reference to Related Applications

This application is a divisional of prior copending application, Serial No. 09/341,764, filed August 19, 1999, which in turn is a 35 U.SC. 371 application of PCT International application No. PCT/FR98/00154, filed January 28, 1998, which in turn claims priority from French application No. 97/00870, filed January 28, 1997.--

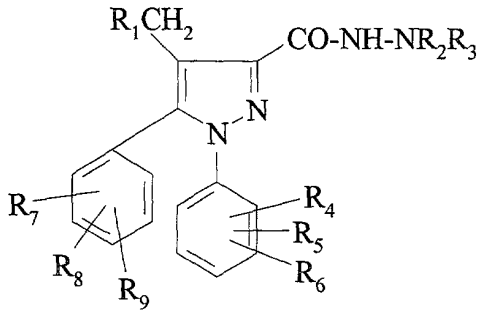
In the claims:

Please cancel claims 1-18 and 34-38, amend claims 19-27 and 32-33, and add new claim 39 as follows before calculating the filing fee for the above-identified application.

19. (amended) A pharmaceutical composition containing a CB_1 receptor antagonist and a regulator of metabolic functions together with a pharmaceutical excipient.

20. (amended) A pharmaceutical composition according to claim 19 wherein said regulator of metabolic functions is a β_3-agonist.

21. (amended) A pharmaceutical composition according to claim 20 wherein the CB_1 receptor antagonist is a compound of the formula



(II)

in which:

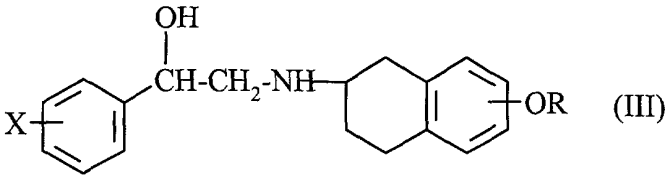
- R_1 is hydrogen, a fluorine, a hydroxyl, a $(C_1$-$C_5)$alkoxy, a $(C_1$-$C_5)$alkylthio, a hydroxy$(C_1$-$C_5)$alkoxy, a group $-NR_{10}R_{11}$, a cyano, a $(C_1$-$C_5)$alkylsulfonyl or a $(C_1$-$C_5)$alkylsulfinyl;
- R_2 and R_3 are a $(C_1$-$C_4)$alkyl or, together with the nitrogen atom to which they are bonded, form a saturated or unsaturated 5- to 10-membered heterocyclic radical which is unsubstituted or monosubstituted or polysubstituted by a $(C_1$-$C_3)$alkyl or by a $(C_1$-$C_3)$alkoxy;
- R_4, R_5, R_6, R_7, R_8 and R_9 are each independently hydrogen, a halogen or a trifluoromethyl, and if R_1 is a fluorine, R_4, R_5, R_6, R_7, R_8 and/or R_9 can also be a fluoromethyl, with the proviso that at least one of the substituents R_4 or R_7 is other than hydrogen;
- R_{10} and R_{11} are each independently hydrogen or a $(C_1$-$C_5)$alkyl, or R_{10} and R_{11}, together with the nitrogen atom to which they are bonded, form a heterocyclic radical selected from pyrrolidin-1-yl, piperidin-1-yl, morpholin-4-yl and piperazin-1-yl, which is unsubstituted or substituted by a $(C_1$-$C_4)$alkyl,

one of its salts or one of their solvates.

22. (amended) A pharmaceutical composition according to claim 21 wherein the CB_1 receptor antagonist is N-piperidino-5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-4-methylpyrazole-3-carboxamide, one of its pharmaceutically acceptable salts or one of their solvates.

23. (amended) A pharmaceutical composition according to claim 21 wherein the β_3-agonist is a

compound of the formula



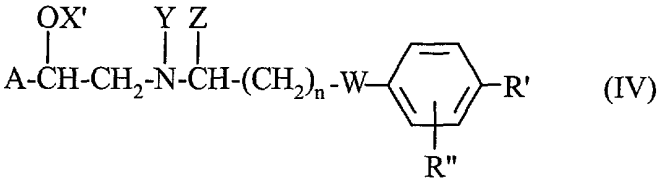
(III)

in which:

- X is hydrogen, a halogen, a trifluoromethyl or a (C_1-C_4)alkyl;
- R is hydrogen or a methyl which is unsubstituted or substituted by a carboxyl or an alkoxycarbonyl in which the alkoxy is (C_1-C_6),

or one of its pharmaceutically acceptable salts.

24. (amended) A pharmaceutical composition according to claim 21 wherein the β_3-agonist is a compound of the formula



(IV)

in which:

- n is 1, 2 or 3;
- A is a benzofuran-2-yl or a phenyl which is unsubstituted or substituted by one or two halogen atoms or by a (C_1-C_4)alkyl or a trifluoromethyl;
- R′ is:
  - hydrogen;
  - a (C_1-C_6)alkyl;
  - a functional group selected from the following groups: hydroxyl; (C_1-C_6)alkoxy; (C_2-C_6)alkenyloxy; (C_2-C_6)alkynyloxy; (C_3-C_8)cycloalkoxy; (C_3-C_8)cycloalkyl(C_1-C_6)alkoxy; benzyloxy; phenoxy; mercapto; (C_1-C_6)alkylthio; (C_2-C_6)alkenylthio; (C_2-C_6)alkynylthio; (C_3-C_8)cycloalkylthio; (C_3-C_8)cycloalkyl(C_1-C_6)alkylthio; benzylthio; phenylthio; (C_1-C_6)alkylsulfinyl; (C_2-C_6)alkenylsulfinyl; (C_2-C_6)alkynylsulfinyl; (C_3-C_8)cycloalkylsulfinyl; (C_3-C_8)cycloalkyl(C_1-C_6)alkylsulfinyl; benzylsulfinyl; phenylsulfinyl; (C_1-C_6)alkylsulfonyl;

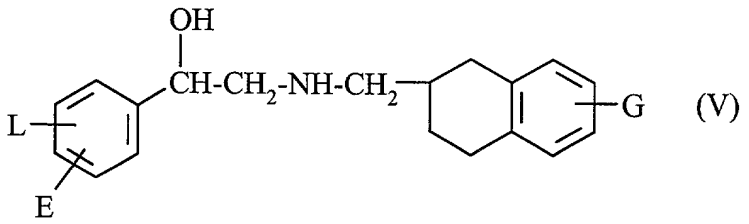
(C_2-C_6)alkenylsulfonyl; (C_2-C_6)alkynylsulfonyl; (C_3-C_8)cycloalkylsulfonyl; (C_3-C_8)-cycloalkyl(C_1-C_6)alkylsulfonyl; benzylsulfonyl; phenylsulfonyl; cyano; nitro; amino which is unsubstituted or substituted by one or two identical or different radicals selected from (C_1-C_6)alkyl, (C_2-C_6)alkenyl, (C_2-C_6)alkynyl, (C_3-C_8)cycloalkyl, (C_3-C_8)cycloalkyl(C_1-C_6)alkyl, benzyl and phenyl groups; carboxyl; alkoxycarbonyl in which the alkoxy is (C_1-C_6); (C_2-C_6)alkenyloxycarbonyl; (C_2-C_6)alkynyloxycarbonyl; (C_3-C_8)cycloalkoxycarbonyl; (C_3-C_8)cycloalkyl(C_1-C_6)alkoxycarbonyl; benzyloxycarbonyl; phenoxycarbonyl; and carbamoyl which is unsubstituted or substituted on the amino group by one or two identical or different radicals selected from (C_1-C_6)alkyl, (C_2-C_6)alkenyl, (C_2-C_6)alkynyl, (C_3-C_8)cycloalkyl, (C_3-C_8)cycloalkyl(C_1-C_6)alkyl, benzyl and phenyl groups;

- a group R‴ selected from the following groups: (C_1-C_6)alkyl substituted by a functional group; (C_2-C_6)alkenyl substituted by a functional group; (C_2-C_6)alkynyl substituted by a functional group; phenyl(C_1-C_6)alkyl substituted on the phenyl by a (C_1-C_6)alkyl or by a functional group; phenyl(C_2-C_6)alkenyl substituted on the phenyl by a (C_1-C_6)alkyl or by a functional group; phenyl(C_2-C_6)alkynyl substituted on the phenyl by a (C_1-C_6)alkyl or by a functional group; benzyl substituted on the phenyl by a (C_1-C_6)alkyl or by a functional group; and phenyl which is unsubstituted or substituted by a (C_1-C_6)alkyl or by a functional group, the functional group being as defined above;
- a group O-R‴, S-R‴, SO-R‴ or SO_2-R‴, in which R‴ is as defined above;
- a group NR‴R°, in which R‴ is as defined above and R° is hydrogen or is as defined above for R‴, or R‴ and R°, together with the nitrogen to which they are bonded, form a group selected from pyrrolidino, piperidino and morpholino groups;
- a group COOR‴ or a group CO-SR‴, in which R‴ is as defined above;
- a group CONR‴R°, in which R‴ is as defined above and R° is hydrogen or is as defined above for R‴, or R‴ and R°, together with the nitrogen to which they are bonded, form a group selected from pyrrolidino, piperidino and morpholino groups;
- a group SO_2NR‴R°, in which R‴ is as defined above and R° is hydrogen or is as defined above for R‴, or R‴ and R°, together with the nitrogen to which they are bonded, form a group selected from pyrrolidino, piperidino and morpholino groups;

- R″ is hydrogen; a halogen; a (C_1-C_6)alkyl; a functional group as defined above; a group OR‴, R‴ being as defined above; a group COOR‴, R‴ being as defined above; or a group CONR‴R°, in which R‴ is as defined above and R° is hydrogen or is as defined above for R‴, or R‴ and R°, together with the nitrogen to which they are bonded, form a group selected from pyrrolidino, piperidino and morpholino groups;
- W is a direct bond or an oxygen atom;
- X′ is hydrogen, a (C_1-C_6)alkyl or a (C_1-C_6)alkylcarbonyl;
- Y is hydrogen or a group A′-CH(OH)-CH_2-, A′ being identical to A but other than benzofuran-2-yl; or
- X′ and Y, taken together, form a methylene group optionally substituted by an alkoxycarbonyl in which the alkoxy is (C_1-C_6); an ethylene group optionally substituted by an oxo group; or a 1,3-propylene group;
- Z is hydrogen or a (C_1-C_6)alkyl,

or one of its pharmaceutically acceptable salts.

25. (amended) A pharmaceutical composition according to claim 21 wherein the β_3-agonist is a compound of the formula



(V)

in which:

- E is hydrogen, a (C_1-C_4)alkyl, a (C_1-C_4)alkoxy, a phenyl, a nitro, a halogen atom or a trifluoromethyl;
- L is hydrogen, a (C_1-C_4)alkyl, a (C_1-C_4)alkoxy, a phenyl, a nitro or a halogen atom; or E and L together are a group -CH=CH-CH=CH- or -CH_2-CH_2-CH_2-CH_2-; and
- G is hydrogen, a chlorine atom, a hydroxyl or a group OG′, in which G′ is a (C_1-C_4)alkyl which is unsubstituted or substituted by a hydroxyl, (C_1-C_4)alkoxy, (C_1-C_4)alkoxycarbonyl, carboxyl or (C_3-C_7)cycloalkyl; a (C_3-C_7)cycloalkyl; or a (C_2-C_4)alkanoyl,

or one of its pharmaceutically acceptable salts.

26. (amended) A pharmaceutical composition according to claim 23 wherein the β_3 agonist is N-[(2S)-7-ethoxycarbonylmethoxy-1,2,3,4-tetrahydronaphth-2-yl]-(2R)-2-(3-chlorophenyl)-2-hydroxyethanamine or one of its pharmaceutically acceptable salts.

27. (amended) A pharmaceutical composition according to claim 23 containing from 0.5 to 600 mg of CB_1 receptor antagonist and from 0.5 to 600 mg of β_3-agonist.

32. (amended) A kit according to claim 31 in which said CB_1 receptor antagonist is N-piperidino-5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-4-methylpyrazole-3-carboxamide, one of its pharmaceutically acceptable salts or one of their solvates and said β_3-agonist is N-[(2S)-7-ethoxycarbonylmethoxy-1,2,3,4-tetrahydronaphth-2-yl]-(2R)-2-(3-chlorophenyl)-2-hydroxyethanamine or one of its pharmaceutically acceptable salts.

33. (amended) A kit according to claim 30 in which said active principles are in different packagings.

Please add the following new claim:

39. (added) A pharmaceutical composition according to claim 26 wherein the CB_1 antagonist is N-piperidino-5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-4-methylpyrazole-3-carboxamide or one of its pharmaceutically acceptable salts or one of their solvates.

REMARKS

The specification has been amended in order to provide the appropriate cross-reference to related application information.

Claims 1-18 and 34-38, which are directed to the subject matter which was elected for prosecution and allowed in U.S. application Serial No. 09/341,764, have been canceled.

Claims 19-27 and 32-33 have been rewritten in accordance with U.S. practice, and multiple dependencies have been eliminated from claims 21, 23-27 and 32-33.

New claim 39 is directed to a pharmaceutical composition containing the preferred CB_1 antagonist and B_3 agonist recited separately in composition claims 22 and 26, respectively.

Claims 19-33 and 39 remain in the application

Attached hereto is a marked-up version of the changes made to the specification and claims by the instant amendment. The marked-up version is entitled "Version With Markings To Show Changes Made".

Respectfully submitted,

Dated: January 11, 2002

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Version With Markings to Show Changes Made

In the specification

On page 1, after the title of the invention and before line 2 insert the following cross reference to related application section was inserted:

--Cross Reference to Related Applications

This application is a divisional of prior copending application, Serial No. 09/341,764, filed August 19, 1999, which in turn is a 35 U.SC. 371 application of PCT International application No. PCT/FR98/00154, filed January 28, 1998, which in turn claims priority from French application No. 97/00870, filed January 28, 1997.--

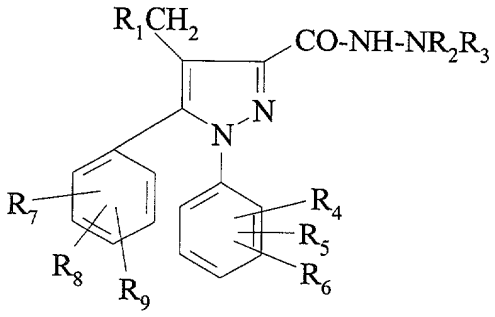
In the Claims:

Claims 19-27 and 32-33 have been amended as follows:

19. (amended) A pharmaceutical composition containing a CB_1 receptor antagonist and a regulator of metabolic functions together with a pharmaceutical excipient.

20. (amended) A pharmaceutical composition according to claim 19[, characterized in that] wherein said regulator of metabolic functions is a β_3-agonist.

21. (amended) A pharmaceutical composition according to claim [19 or] 20[, characterized in that] wherein the CB_1 receptor antagonist is a compound of the formula



(II)

in which:

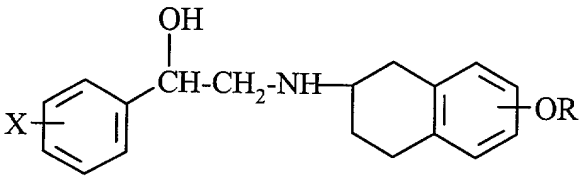
- R_1 is hydrogen, a fluorine, a hydroxyl, a $(C_1$-$C_5)$alkoxy, a $(C_1$-$C_5)$alkylthio, a hydroxy$(C_1$-$C_5)$alkoxy, a group $-NR_{10}R_{11}$, a cyano, a $(C_1$-$C_5)$alkylsulfonyl or a $(C_1$-$C_5)$alkylsulfinyl;

- R_2 and R_3 are a $(C_1$-$C_4)$alkyl or, together with the nitrogen atom to which they are bonded, form a saturated or unsaturated 5- to 10-membered heterocyclic radical which is unsubstituted or monosubstituted or polysubstituted by a $(C_1$-$C_3)$alkyl or by a $(C_1$-$C_3)$alkoxy;
- R_4, R_5, R_6, R_7, R_8 and R_9 are each independently hydrogen, a halogen or a trifluoromethyl, and if R_1 is a fluorine, R_4, R_5, R_6, R_7, R_8 and/or R_9 can also be a fluoromethyl, with the proviso that at least one of the substituents R_4 or R_7 is other than hydrogen;
- R_{10} and R_{11} are each independently hydrogen or a $(C_1$-$C_5)$alkyl, or R_{10} and R_{11}, together with the nitrogen atom to which they are bonded, form a heterocyclic radical selected from pyrrolidin-1-yl, piperidin-1-yl, morpholin-4-yl and piperazin-1-yl, which is unsubstituted or substituted by a $(C_1$-$C_4)$alkyl,

one of its salts or one of their solvates.

22. (amended) A pharmaceutical composition according to claim 21[, characterized in that] wherein the CB_1 receptor antagonist is N-piperidino-5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-4-methylpyrazole-3-carboxamide, one of its pharmaceutically acceptable salts or one of their solvates.

23. (amended) A pharmaceutical composition according to [any one of claims 20 to 22, characterized in that] claim 21 wherein the β_3-agonist is a compound of the formula



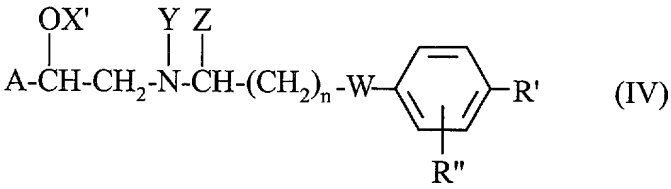
(III)

in which:

- X is hydrogen, a halogen, a trifluoromethyl or a $(C_1$-$C_4)$alkyl;
- R is hydrogen or a methyl which is unsubstituted or substituted by a carboxyl or an alkoxycarbonyl in which the alkoxy is $(C_1$-$C_6)$,

or one of its pharmaceutically acceptable salts.

24. (amended) A pharmaceutical composition according to [any one of claims 20 to 22, characterized in that] claim 21 wherein the β_3-agonist is a compound of the formula



(IV)

in which:

- n is 1, 2 or 3;
- A is a benzofuran-2-yl or a phenyl which is unsubstituted or substituted by one or two halogen atoms or by a (C_1-C_4)alkyl or a trifluoromethyl;
- R′ is:
  - hydrogen;
  - a (C_1-C_6)alkyl;
  - a functional group selected from the following groups: hydroxyl; (C_1-C_6)alkoxy; (C_2-C_6)alkenyloxy; (C_2-C_6)alkynyloxy; (C_3-C_8)cycloalkoxy; (C_3-C_8)cycloalkyl(C_1-C_6)alkoxy; benzyloxy; phenoxy; mercapto; (C_1-C_6)alkylthio; (C_2-C_6)alkenylthio; (C_2-C_6)alkynylthio; (C_3-C_8)cycloalkylthio; (C_3-C_8)cycloalkyl(C_1-C_6)alkylthio; benzylthio; phenylthio; (C_1-C_6)alkylsulfinyl; (C_2-C_6)alkenylsulfinyl; (C_2-C_6)alkynylsulfinyl; (C_3-C_8)cycloalkylsulfinyl; (C_3-C_8)cycloalkyl(C_1-C_6)alkylsulfinyl; benzylsulfinyl; phenylsulfinyl; (C_1-C_6)alkylsulfonyl; (C_2-C_6)alkenylsulfonyl; (C_2-C_6)alkynylsulfonyl; (C_3-C_8)cycloalkylsulfonyl; (C_3-C_8)cycloalkyl(C_1-C_6)alkylsulfonyl; benzylsulfonyl; phenylsulfonyl; cyano; nitro; amino which is unsubstituted or substituted by one or two identical or different radicals selected from (C_1-C_6)alkyl, (C_2-C_6)alkenyl, (C_2-C_6)alkynyl, (C_3-C_8)cycloalkyl, (C_3-C_8)cycloalkyl(C_1-C_6)alkyl, benzyl and phenyl groups; carboxyl; alkoxycarbonyl in which the alkoxy is (C_1-C_6); (C_2-C_6)alkenyloxycarbonyl; (C_2-C_6)alkynyloxycarbonyl; (C_3-C_8)cycloalkoxycarbonyl; (C_3-C_8)cycloalkyl(C_1-C_6)alkoxycarbonyl; benzyloxycarbonyl; phenoxycarbonyl; and carbamoyl which is unsubstituted or

substituted on the amino group by one or two identical or different radicals selected from (C_1-C_6)alkyl, (C_2-C_6)alkenyl, (C_2-C_6)alkynyl, (C_3-C_8)cycloalkyl, (C_3-C_8)-cycloalkyl(C_1-C_6)alkyl, benzyl and phenyl groups;

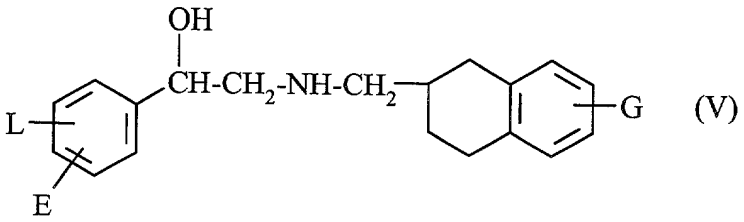
- a group R''' selected from the following groups: (C_1-C_6)alkyl substituted by a functional group; (C_2-C_6)alkenyl substituted by a functional group; (C_2-C_6)alkynyl substituted by a functional group; phenyl(C_1-C_6)alkyl substituted on the phenyl by a (C_1-C_6)alkyl or by a functional group; phenyl(C_2-C_6)alkenyl substituted on the phenyl by a (C_1-C_6)alkyl or by a functional group; phenyl(C_2-C_6)alkynyl substituted on the phenyl by a (C_1-C_6)alkyl or by a functional group; benzyl substituted on the phenyl by a (C_1-C_6)alkyl or by a functional group; and phenyl which is unsubstituted or substituted by a (C_1-C_6)alkyl or by a functional group, the functional group being as defined above;
- a group O-R''', S-R''', SO-R''' or SO_2-R''', in which R''' is as defined above;
- a group NR'''R°, in which R''' is as defined above and R° is hydrogen or is as defined above for R''', or R''' and R°, together with the nitrogen to which they are bonded, form a group selected from pyrrolidino, piperidino and morpholino groups;
- a group COOR''' or a group CO-SR''', in which R''' is as defined above;
- a group CONR'''R°, in which R''' is as defined above and R° is hydrogen or is as defined above for R''', or R''' and R°, together with the nitrogen to which they are bonded, form a group selected from pyrrolidino, piperidino and morpholino groups;
- a group SO_2NR'''R°, in which R''' is as defined above and R° is hydrogen or is as defined above for R''', or R''' and R°, together with the nitrogen to which they are bonded, form a group selected from pyrrolidino, piperidino and morpholino groups;

- R'' is hydrogen; a halogen; a (C_1-C_6)alkyl; a functional group as defined above; a group OR''', R''' being as defined above; a group COOR''', R''' being as defined above; or a group CONR'''R°, in which R''' is as defined above and R° is hydrogen or is as defined above for R''', or R''' and R°, together with the nitrogen to which they are bonded, form a group selected from pyrrolidino, piperidino and morpholino groups;
- W is a direct bond or an oxygen atom;
- X' is hydrogen, a (C_1-C_6)alkyl or a (C_1-C_6)alkylcarbonyl;

- Y is hydrogen or a group A′-CH(OH)-CH_2-, A′ being identical to A but other than benzofuran-2-yl; or
- X′ and Y, taken together, form a methylene group optionally substituted by an alkoxycarbonyl in which the alkoxy is (C_1-C_6); an ethylene group optionally substituted by an oxo group; or a 1,3-propylene group;
- Z is hydrogen or a (C_1-C_6)alkyl,

or one of its pharmaceutically acceptable salts.

25. (amended) A pharmaceutical composition according to [any one of claims 20 to 22] claim 21 wherein the β_3-agonist is a compound of the formula



(V)

in which:

- E is hydrogen, a (C_1-C_4)alkyl, a (C_1-C_4)alkoxy, a phenyl, a nitro, a halogen atom or a trifluoromethyl;
- L is hydrogen, a (C_1-C_4)alkyl, a (C_1-C_4)alkoxy, a phenyl, a nitro or a halogen atom; or E and L together are a group -CH=CH-CH=CH- or -CH_2-CH_2-CH_2-CH_2-; and
- G is hydrogen, a chlorine atom, a hydroxyl or a group OG′, in which G′ is a (C_1-C_4)alkyl which is unsubstituted or substituted by a hydroxyl, (C_1-C_4)alkoxy, (C_1-C_4)alkoxycarbonyl, carboxyl or (C_3-C_7)cycloalkyl; a (C_3-C_7)cycloalkyl; or a (C_2-C_4)alkanoyl,

or one of its pharmaceutically acceptable salts.

26. (amended) A pharmaceutical composition according to claim 23[, characterized in that] wherein the β_3 agonist is N-[(2S)-7-ethoxycarbonylmethoxy-1,2,3,4-tetrahydronaphth-2-yl]-(2R)-2-(3-chlorophenyl)-2-hydroxyethanamine or one of its pharmaceutically acceptable salts.

27. (amended) A pharmaceutical composition according to [any one of claims 20 to 26] claim 23 containing from 0.5 to 600 mg of CB_1 receptor antagonist and from 0.5 to 600 mg of β_3-agonist.

32. (amended) A kit according to claim [30 or] 31 in which said CB_1 receptor antagonist is N-piperidino-5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-4-methylpyrazole-3-carboxamide, one of its pharmaceutically acceptable salts or one of their solvates and said β_3-agonist is N-[(2S)-7-ethoxycarbonylmethoxy-1,2,3,4-tetrahydronaphth-2-yl]-(2R)-2-(3-chlorophenyl)-2-hydroxyethanamine or one of its pharmaceutically acceptable salts.

33. (amended) A kit according to [any one of claims 30 to 32] claim 30 in which said active principles are in different packagings.

Claims 1-18 and 34-38 have been canceled.

New claim 39 has been added.